"transferred" has been corrected. At page 107, the spelling of "Recombinant" has been corrected.

Claims 1-158 will be pending and under consideration upon entry of this amendment. Claims 124, 134, 146 and 153 have been amended to correct inadvertent typographical errors. Claims 124 has been amended to correct the spelling of "endogenous" and "channel subfamily". Claim 134 has been amended to correct the spelling of "endogenous." Claim 146 has been amended to delete a duplication of the word "pure." Claim 153 has been amended to correct the spelling of "administered."

A marked up version of replacement paragraphs of the specification indicating the changes made is attached as Exhibit A. A marked version of the claims indicating the changes made is attached as Exhibit B. A copy of all the claims, as amended, is attached as Exhibit C. The amendments are fully supported by the present specification and by the original claims as filed.

No new matter is added by way of the amendments to the specification or claims.

CONCLUSION

Applicants respectfully request the entry of the foregoing amendments and remarks into the file history of the present application.

Respectfully submitted,

Dated: August 20, 2001

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Attachments:

Exhibit A:	Marked Up Version of Replacement Paragraphs of the Specification
Exhibit B:	Marked Up Version of the Amended Claims
Exhibit C:	Claims Pending after Entry of the Preliminary Amendment Dated August 20, 2001

EXHIBIT A

Marked Up Version of Replacement Paragraphs of the Specification

U.S. Patent Application Serial No. 09/783,487

Matter that has been deleted from the paragraphs is indicated by brackets and matter that has been added to the paragraphs is indicated by double underlining. Matter that was originally underlined in the paragraphs remains singly underlined to distinguish it from matter that has been added.

At page 20, line 9, please amend the paragraph beginning "In certain embodiments," as follows:

In certain embodiments, the system gene coding sequences are to be inserted in a site in the characterizing gene sequences other than the 5' start site of the characterizing gene coding sequences, for example, in the 3' most translated or untranslated regions. In these embodiments, the clones containing the characterizing gene should be mapped to insure the clone contains the site for insertion in as well as sufficient sequence 5' of the characterizing gene coding sequences library to contain the regulatory sequences necessary to direct expression of the system gene sequences in the same expression pattern as the [endogneous] endogenous characterizing gene.

At page 58, line 23, please amend the paragraph beginning "In other embodiments," as follows:

In other embodiments, the characterizing gene sequence is protein kinase C, gamma (GenBank Accession Number: Z15114 (human); MGI Database Accession Number: MGI:97597); fos (Unigene No. MM5043 (mouse)); TH-elastin; Pax7 (Mansouri, 1998, The role of Pax3 and Pax7 in development and cancer, Crit. Rev. Oncog. 9(2):141-9); Eph receptor (Mellitzer *et al.*, 2000, Control of cell behaviour by signalling through Eph receptors and ephrins; [Cur.r] Curr. Opin. Neurobiol. 10(3):400-08; Suda *et al.*, 2000, Hematopoiesis and angiogenesis, Int. J. Hematol. 71(2):99-107; Wilkinson, 2000, Eph receptors and ephrins: regulators of guidance and assembly, Int. Rev. Cytol. 196:177-244; Nakamoto, 2000, Eph receptors and ephrins, Int. J. Biochem. Cell Biol. 32(1):7-12; Tallquist *et al.*, 1999, Growth factor signaling pathways in vascular development, Oncogene 18(55):7917-32); islet-1 (Bang et al., 1996, Regulation of vertebrate neural cell fate by

transcription factors, Curr. Opin. Neurobiol. 6(1):25-32; Ericson *et al.*, 1995, Sonic hedgehog: a common signal for ventral patterning along the rostrocaudal axis of the neural tube, J. Dev. Biol. 39(5):809-16; β-actin; thy-1 (Caroni, 1997, Overexpression of growth-associated proteins in the neurons of adult transgenic mice, J. Neurosci. Methods 71(1):3-9).

At page 59, line 4, please amend the paragraph beginning "As discussed above in Section 4.2," as follows:

As discussed above in Section 4.2, the [trangenes] transgenes of the invention include all or a portion of the characterizing gene genomic sequence, preferably at least all or a portion of the upstream regulatory sequences of the characterizing gene genomic sequences are present in the transgene, and at a minimum, the characterizing [gen] gene sequences that direct expression of the system gene coding sequences in substantially the same pattern as the endogenous characterizing gene in the transgenic mouse or anatomical region or tissue thereof are present on the transgene.

On pages 61-62, beginning at page 61, line 26, please amend the paragraph beginning "The system gene coding sequences" as follows:

The system gene coding sequences can be present at a low gene dose, such as one copy of the system gene per cell. In other embodiments, at least two, three, five, seven, ten or more copies of the system gene coding sequences are present per cell, *e.g.*, multiple copies of the system gene coding sequences are present in the same transgene or are present in one copy in the transgene and more than one transgene is present in the cell. In a specific embodiment in which BACs are used to generate and introduce the transgene into the animal, the gene dosage is one copy of the system gene per BAC and at least two, three, five, seven, ten or more copies of the BAC per cell. More then one copy of the system gene coding sequences may be necessary in some instances to achieve detectable or selectable levels of the marker gene. In cases where the transgene is present at high copy numbers or even in certain circumstances when it is present at one copy per cell, coding sequences other than the system gene coding sequences, for example, the characterizing gene coding sequence, if present, and/or any other protein coding sequences (for example, from other genes proximal to the characterizing gene in the genomic DNA) are [inactiviated] inactivated to avoid over- or mis-expression of these other gene products.

At page 62, line 16, please amend the paragraph beginning "In specific embodiments," as follows:

In specific embodiments, the system gene encodes β-lactamase (*e.g.*, GeneBLAzer™ Reporter System, Aurora Biosciences), *E. coli* β-galactosidase (lacZ, InvivoGen), human placental alkaline phosphatase (PLAP, InvivoGen) (Kam *et al.*,1985, Proc. Natl. Acad. Sci. USA 82: 8715-19), *E. coli* β-glucuronidase (gus, Sigma) (Jefferson *et al.*, 1986, Proc. Natl. Acad. Sci 83:8447-8451) alkaline phosphatase, horseradish peroxidase, with β-lactamase being particularly preferred (Zlokarnik *et al.*, 1998, Science 279: 84-88; incorporated herein by reference in its entirety). In other embodiments, the system gene encodes a [chemiluminscent] chemiluminescent enzyme marker such as luciferase (Danilov *et al.*, 1989, Bacterial luciferase as a biosensor of biologically active compounds. Biotechnology, 11:39-78; Gould *et al.*, 1988, Firefly luciferase as a tool in molecular and cell biology, Anal. Biochem.175(1):5-13; Kricka, 1988, Clinical and biochemical applications of luciferases and luciferins, Anal. Biochem. 175(1):14-21; Welsh *et al.*, 1997, Reporter gene expression for monitoring gene transfer, Curr. Opin. Biotechnol. 8(5):617-22; Contag *et al.*, 2000, Use of reporter genes for optical measurements of neoplastic disease in vivo, Neoplasia 2(1-2):41-52; Himes *et al.*, 2000, Assays for transcriptional activity based on the luciferase reporter gene, Methods Mol. Biol. 130:165-74; Naylor *et al.*, 1999, Reporter gene technology: the future looks bright, Biochem. Pharmacol. 58(5):749-57, all of which are incorporated by reference in their entireties).

At page 67, line 5, please amend the paragraph beginning "In a specific embodiment," as follows:

In a specific embodiment, the ligand-regulated recombinase system of Kellendonk *et al.* (1999, J. Mol. Biol. 285: 175-82; incorporated herein by reference in its entirety) can be used. In this system, the ligand-binding domain (LBD) of a receptor, *e.g.*, the progesterone or estrogen receptor, is fused to the Cre recombinase to increase [specifity] specificity of the recombinase.

On pages 74-75, beginning at page 74, line 35, please amend the paragraph beginning "A vector containing a transgene" as follows:

A vector containing a transgene can be introduced into the desired host cell by methods known in the art, *e.g.*, transfection, transformation, transduction, electroporation, infection, microinjection, cell fusion, DEAE dextran, calcium phosphate precipitation, liposomes, LIPOFECTIN™[(source)], lysosome fusion, synthetic cationic lipids, use of a gene gun or a DNA vector transporter, such that the transgene is transmitted to offspring in the line. For various techniques for transformation or transfection of mammalian cells, see Keown *et al.*, 1990, Methods Enzymol. 185: 527-37; Sambrook *et al.*, 2001, Molecular Cloning, A Laboratory Manual, Third Edition, Cold Spring Harbor Laboratory Press, N.Y.

At page 76, line 4, please amend the paragraph beginning "Preferably, the transgene is introduced" as follows:

Preferably, the transgene is introduced using any technique so long as it is not destructive to the [cell,nuclear] cell, nuclear membrane or other existing cellular or genetic structures. The transgene is preferentially inserted into the nucleic genetic material by microinjection. Microinjection of cells and cellular structures is known and is used in the art. Also known in the art are methods of transplanting the embryo or zygote into a pseudopregnant female where the embryo is developed to term and the transgene is integrated and expressed. See, *e.g.*, Hogan *et al.* 1986, *Manipulating the Mouse Embryo,* Cold Spring Harbor Laboratory Press, New York, NY.

On pages 79-80, beginning at page 79, line 32, please amend the paragraph beginning "The selected ES cells" as follows:

The selected ES cells are then injected into a blastocyst of an animal (*e.g.*, a mouse) to form aggregation chimeras. *See, e.g.,* Bradley, 1987, in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, Robertson, ed., IRL, Oxford, 113-52. Blastocysts are obtained from 4 to 6 week old superovulated females. The ES cells are trypsinized, and the modified cells are injected into the blastocoel of the blastocyst. After injection, the blastocysts are implanted into the uterine horns of suitable pseudopregnant female foster animal. Alternatively, the ES cells may be incorporated into a morula to form a morula aggregate which is then implanted into a suitable pseudopregnant [femal] female foster animal. Females are then allowed to go to term and the resulting litters screened for mutant cells having the construct.

On pages 80-81, beginning at page 80, line 21, please amend the paragraph beginning "Once the transgenic mice" as follows:

Once the transgenic mice are generated they may be bred and maintained using methods well known in the art. By way of example, the mice may be housed in an environmentally controlled facility maintained on a 10 hour dark: 14 hour light cycle or other appropriate light cycle. Mice are mated when they are sexually mature (6 to 8 weeks old). In certain embodiments, the transgenic founders or chimeras are mated to an unmodified animal (*i.e.*, an animal having no cells containing the transgene). In a preferred embodiment, the transgenic founder or chimera is mated to C57BL/6 mice (Jackson Laboratories). In a specific embodiment where the transgene is introduced into ES cells and a chimeric mouse is generated, the chimera is mated to 129/Sv mice, which have the same genotype as the embryonic stem cells. Protocols for successful breeding are known in the art (See [hhtp://www.informatics.jax.org/mgihome] <u>http://www.informatics.jax.org/mgihome</u>). Preferably, a founder male is mated with two females and a founder female is mated with one male. Preferably two females are rotated through a male's cage every 1-2 weeks. Pregnant females are generally housed 1 or 2 per cage. Preferably, pups are ear tagged, genotyped, and weaned at approximately 21 days. Males and females are housed separately. Preferably log sheets are kept for any mated animal, by example and not limitation, information should include pedigree, birth date, sex, ear tag number, source of mother and father, genotype, dates mated and generation.

At page 81, line 4, please amend the paragraph beginning "More specifically" as follows:

More specifically, founder animals heterozygous for the transgene may be mated to generate a homozygous line as follows: A [heterzygous] <u>heterozygous</u> founder animal, designated as the P_1 generation, is mated with an offspring designated as the F_1 generation from a mating of a non-transgenic mouse with a transgenic mouse heterozygous for the transgene (backcross). Based on classical genetics, one fourth of the results of this backcross are homozygous for the transgene. In a preferred embodiment, transgenic founders are individually backcrossed to an inbred or outbred strain of choice. Different founders should not be intercrossed, since different expression patterns may result from separate transgene integration events.

At page 86, line 25, please amend the paragraph beginning "In one embodiment of the invention" as follows:

In one embodiment of the invention, cells are isolated by FACS using fluorescent antibody staining of cell surface proteins. The cells are isolated using methods known in the art as described by Barrett *et al.*, 1998, *Neuroscience*, 85(4):1321-8, incorporated herein in its entirety. In another embodiment, cells are isolated by FACS using fluorogenic substrates of an enzyme transgenically expressed in a particular cell-type. The cells are isolated using methods known in the art as described by Blass-Kampmann *et al.*, 1994, *J. Neurosci. Res.,* 37(3):359-73, which is incorporated herein by reference in its [entirerty] entirety.

At page 88, line 11, please amend the paragraph beginning "Additionally, the transgenic animals" as follows:

Additionally, the transgenic animals may be bred to existing disease model animals or treated [pharmacogically] pharmacologically or surgically, or by any other means, to create a disease state in the transgenic animal. The marked population of cells can then be compared in the animal having and not having the disease state. Additionally, treatments for the disease may be evaluated by administering the treatment (*e.g.*, a candidate compound) to the transgenic mice of the invention that have been bred to a disease state or a disease model otherwise induced in the transgenic mice and then detecting the marked population of cells. Changes in the marked population of cells are assayed, for example, for morphological, physiological or electrophysiological changes, changes in gene expression, protein-protein interactions, protein profile in response to the treatment is an indication of efficacy or toxicity, etc., of the treatment.

On pages 88-89, beginning at page 88, line 34, please amend the paragraph beginning "Once isolated" as follows:

Once isolated, the populations of cells can be analyzed by any method known in the art. In one aspect of the invention, the gene expression profile of the cells is analyzed using any number of methods known in the art, for example but not by way of limitation, by isolating the mRNA from the isolated cells and then hybridizing the [cells] mRNA to a microarray to identify the genes which are or are not expressed in the isolated cells. Gene expression in cells treated and not treated with a compound of interest or in

cells from animals treated or untreated with a particular treatment may be compared. In addition, mRNA from the isolated cells may also be analyzed, for example by northern blot analysis, PCR, RNase protection, etc., for the presence of mRNAs encoding certain protein products and for changes in the presence or levels of these mRNAs depending on the treatment of the cells. In another aspect, mRNA from the isolated cells may be used to produce a cDNA library and, in fact, a collection of such cell type specific cDNA libraries may be generated from different populations of isolated cells. Such cDNA libraries are useful to analyze gene expression, isolate and identify cell type-specific genes, splice variants and non-coding RNAs. In another aspect, such cell type specific libraries prepared from cells isolated from treated and untreated transgenic animals of the invention or from transgenic animals of the invention having and not having a disease state can be used, for example in subtractive hybridization procedures, to identify genes expressed at higher or lower levels in response to a particular treatment or in a disease state as compared to untreated transgenic animals. Data from such analyses may be used to generate a database of gene expression analysis for different populations of cells in the animal or in particular tissues or anatomical regions, for example, in the brain. Using such a database together with bioinformatics tools, such as hierarchical and non-hierarchical clustering analysis and [pricipal] principal components analysis, cells are "fingerprinted" for particular indications from healthy and disease-model animals or tissues.

On pages 91-92, beginning at page 91, line 35, please amend the paragraph beginning "1. Target BAC clone DNA" as follows:

1. Target BAC clone DNA immobilized on nylon filters, for [example,a] example, a macroarray of a BAC library, *e.g.*, the CITB BAC library (Research Genetics) or the RPCI-23 library (BACPAC Resources, Children's Hospital Oakland Research Institute, Oakland, CA).

On pages 98-99, beginning at page 98, line 26, please amend the paragraph beginning "A mouse BAC library" as follows:

A mouse BAC library, *e.g.*, a RPCI-23 BAC library, can be fingerprinted using the methods of Soderlund *et al.* (2000, Genome Res. 10(11):1772-87; incorporated herein by reference in its entirety). BACs are fingerprinted using HindIII digestion digests. Digests are run out on 1% agarose gels, stained with sybr green (Molecular Probes) and then

visualized on a Typhoon fluoroimager (Amersham Pharmacia). Gel image data is acquired using the "IMAGE" program (Sanger Center; http://www.sanger.ac.uk/). Data from "IMAGE" is then passed along to the analysis program "FPC" ([fingerpring] fingerprinting contig)(Sanger Center; http://www.sanger.ac.uk/). Using FPC, the data from a publicly available genome database can be queried to determine if the insert of a particular BAC has been fingerprinted and contigged. BAC fingerprint information has been generated by the University of British Columbia Genome Mapping Project (http://www.bcgsc.bc.ca/projects/mouse_mapping) and can be used for assembling BAC contigs. Preferably, contig information from publicly available databases is used to select clones for BAC modification as described above.

At page 101, line 19, please amend the paragraph beginning "8. The membrane is prewet" as follows:

8. The membrane is prewet with [with] ddH_2O. The membrane is prehybridized in hybridization buffer at 37°C for 10 min. For the prehybridization and hybridization steps, exactly 50 μl of buffer is used per 1.0 cm^2 of membrane.

At page 106, line 4, please amend the paragraph beginning "1ml SOC is added" as follows:

1ml SOC is added to each cuvette immediately after conducting the electroporation. The cells are resuspended. The cell suspension is [transfered] transferred to a 17x100mm polypropylene tube and incubated at 37°C for one hour with shaking at 225 RPM.

At page 107, line 1, please amend the paragraph beginning "**Identification and Purification of Recombinatnt BAC DNA**" as follows:

Identification and Purification of [Recombinatnt] Recombinant BAC DNA

BAC DNA is purified as follows and is then used for pronuclear injection or other methods known in the art to create transgenic mice.

EXHIBIT B

Marked Up Version of the Amended Claims

U.S. Patent Application Serial No. 09/783,487

Matter that has been deleted from the claims is indicated by brackets and matter that has been added to the claims is indicated by double underlining.

124 (amended). A transgenic animal comprising a transgene, said transgene comprising (a) first sequences coding for a selectable or detectable marker protein; and (b) regulatory sequences of a characterizing gene corresponding to an endogenous gene or ortholog of an endogenous gene operably linked to said first sequences such that said first sequences are expressed in said transgenic animal with an expression pattern that is substantially the same as the expression pattern of said endogenous gene in a non-transgenic animal or anatomical region thereof, wherein said transgene is present in the genome at a site other than where the [endogneous] endogenous gene is located, said characterizing gene being ADRB1, ADRB2, ADRB3, ADRA1A, ADRA1B, ADRA1C, ADRA1D, ADRA2A, ADRA2B, ADRA2C, SLC6A2, Norepinephrine transporter, CHRM1 (Muscarinic Ach M1) receptor, CHRM2 (Muscarinic Ach M2) receptor, CHRM3 (Muscarinic Ach M3) receptor, CHRM4 (Muscarinic Ach M4) receptor, CHRM5 (Muscarinic Ach M5) receptor, CHRNA1 (nicotinic alpha1) receptor, CHRNA2 (nicotinic alpha2) receptor, CHRNA3 (nicotinic alpha3) receptor, CHRNA4 (nicotinic alpha4) receptor, CHRNA5 (nicotinic alpha5) receptor, CHRNA7 (nicotinic alpha7) receptor, CHRNB1 (nicotinic Beta 1) receptor, CHRNB2 (nicotinic Beta 2) receptor, CHRNB3 (nicotinic Beta 3) receptor, CHRNB4 (nicotinic Beta 4) receptor, CHRNG nicotinic gamma immature muscle receptor, CHRNE nicotinic epsilon receptor, CHRND nicotinic delta receptor, tyrosine hydroxylase, dopamine transporter, dopamine receptor 1, dopamine receptor 2, dopamine receptor 3, dopamine receptor 4, dopamine receptor 5, dbh, dopamine beta hydroxylase, GABA receptor A2, GABA receptor A3, GABA receptor A4, GABA receptor A5, GABA receptor A6, GABA receptor B1, GABA receptor B2, GABA receptor B3, GABA-A receptor (gamma 1subunit), GABA-A receptor (gamma 2 subunit), GABA-A receptor (gamma 3 subunit), GABA-A receptor (delta subunit), GABA-A receptor (epsilon subunit), GABA-A receptor (pi subunit), GABA receptor theta, GABA receptor rho 1, GluR1, GlurR2, GluR3, GluR4, GluR5, GluR6, GluR7, GRIK4 (KA1), GRIK5 (KA2),

NMDA receptor 1, NMDA receptor 2A, NMDA receptor 2B, NMDA receptor 2C, NMDA receptor 2D, mGluR1a, mGluR2, mGluR3, mGluR4, mGluR5, mGluR6, mGluR7, mGluR8, glut ionotropic delta, glutamate/aspartate transporter II, glutamate transporter GLT1, glutamate transporter SLC1A2, glial high affinity glutamate transporter, neuronal/epithelial high affinity glutamate transporter, glial high affinity glutamate transporter, high affinity aspartate/glutamate transporter, Glycine receptors alpha 1, Glycine receptors alpha 2, Glycine receptors alpha 3, Glycine receptors alpha 4, glycine receptor beta, histamine H1-receptor 1, Histamine H2-receptor 2, Histamine H3-receptor 3, orexin OX-A, Orexin receptor OX1R, Orexin receptor OX2R, Leptin receptor long form, melanin concentrating hormone, melanocortin 3 receptor, melanocortin 4 receptor, melanocortin 5 receptor, corticotropin releasing hormone, CRH/CRF receptor 1, CRH/CRF receptor 2, CRF binding protein, Urocortin, Pro-opiomelanocortin, cocaine and amphetamine regulated transcript, Neuropeptide Y, Neuropeptide Y1 receptor, Neuropeptide Y2 receptor, Npy4R Neuropeptide Y4 receptor, Npy5R Neuropeptide Y5 receptor, Npy6r Neuropeptide Y receptor, cholecystokinin, CCKAR cholecystokinin receptor, CCKBR cholecystokinin receptor, agouti related peptide, Galanin, Galanin like peptide, galanin receptor1, galanin receptor2, galanin receptor3, prepro-urotensin II, Urotensin receptor, somatostatin, somatostatin receptor sst1, somatostatin receptor sst2, somatostatin receptor sst3, somatostatin receptor sst4, somatostatin receptor sst5, G protein-coupled receptor 7, opioid-somatostatin-like receptor, G protein-coupled receptor 8 opioid-somatostatin-like receptor, pre Pro Enkephalin, Pre pro Dynorphin, μ opiate receptor, kappa opiate receptor, delta opiate receptor, ORL1 opioid receptor-like receptor, Vanilloid receptor subtype 1, protein 1 VRL1, vanilloid receptor-like protein 1, vanilloid receptor-related osmotically activated channel, cannaboid receptors CB1, endothelin 1 ET-1growth hormone releasing hormone, growth hormone releasing hormone receptor, nociceptin orphanin FQ/nocistatin, neuropeptide FF precursor, G-protein coupled receptor NPGPR, gastrin releasing peptide, preprogastrin-releasing peptide, gastrin releasing peptide receptor BB2, neuromedin B, neuromedin B receptor BB1, bombesin like receptor subtype-3, uterine bombesin receptor, GCG PROglucagon, glucagon receptor, GLP1 receptor, GLP2 receptor, vasoactive intestinal peptide, secretin, pancreatic polypeptide receptor 1, pre-pro-Oxytocin, oxytocin receptor, Preprovasopressin, vasopressin receptor 1a, vasopressin receptor 1b, vasopressin receptor 2, Neurotensin tridecapeptide plus neuromedin N, Neurotensin receptor NT1, Neurotensin receptor NT2, sortilin 1 neurotensin receptor 3, Bradykinin receptor 1,

Bradykinin receptor B2, gonadotrophin releasing hormone, gonadotrophin releasing hormone, gonadotrophin releasing hormone receptor, calcitonin-related polypeptide, beta, calcitonin/calcitonin-related polypeptide alpha, calcitonin receptor, neurokinin A, neurokinin B, neurokinin a (subK) receptor, tachykinin receptor NK2 (Sub P and K), tachykinin receptor NK3 (Sub P and K) neuromedin K, PACAP, atrial naturietic peptide (ANP) precursor, atrial naturietic peptide (BNP) precursor, naturietic peptide receptor 1, naturietic peptide receptor 2, naturietic peptide receptor 3, VIP receptor 1, PACAP receptor, serotonin receptor 1A, serotonin receptor 2A, serotonin receptor 3, serotonin receptor 1B, serotonin receptor 1D, serotonin receptor 1E, serotonin receptor 2B, serotonin receptor 2C, serotonin receptor 4, serotonin receptor 5A, serotonin receptor 5B, serotonin receptor 6, serotonin receptor 7, serotonin transporter, tryptophan hydroxylase, purinergic receptor P2X ligand-gated ion channel, purinergic receptor P2X ligand-gated ion channel 3, purinergic receptor P2X ligand-gated ion channel 4, purinergic receptor P2X ligand-gated ion channel 5, purinergic receptor P2X-like 1 orphan receptor, purinergic receptor P2X ligand-gated ion channel 7, purinergic receptor P2Y G-protein coupled 1, purinergic receptor P2Y G-protein coupled 2, pyrimidinergic receptor P2Y G-protein coupled 4, pyrimidinergic receptor P2Y G-protein coupled 6, purinergic receptor P2Y G-protein coupled 11, voltage gated sodium channel type I alpha, sodium channel voltage-gated type I beta, sodium channel voltage-gated type II beta, sodium channel voltage-gated type V alpha, sodium channel voltage-gated type II alpha 1, sodium channel voltage-gated type II alpha 2, sodium channel voltage-gated type III alpha, sodium channel voltage-gated type IV alpha, sodium channel voltage-gated type VII or VI, sodium channel voltage-gated type VIII, sodium channel voltage-gated type IX alpha, sodium channel voltage-gated type X, sodium channel voltage-gated type XI alpha, sodium channel voltage-gated type XII alpha, sodium channel nonvoltage-gated 1 alpha, sodium channel voltage-gated type IV beta, sodium channel nonvoltage-gated 1 beta, sodium channel nonvoltage-gated 1 delta, sodium channel nonvoltage-gated 1 gamma, chloride channel 1 skeletal muscle, chloride channel 2, chloride channel 3, chloride channel 4, chloride channel 5, chloride channel 6, chloride channel 7, chloride intracellular channel 1, chloride intracellular channel 2, chloride intracellular channel 3, chloride intracellular channel 5, chloride channel Kb, chloride channel Ka, chloride channel, calcium activated family member 1, chloride channel calcium activated family member 2, chloride channel calcium activated family member 3, chloride channel calcium activated family member 4, potassium voltage-gated channel shaker-related

subfamily member 1, potassium voltage-gated channel shaker-related subfamily member 2, potassium voltage-gated channel shaker-related subfamily member 3, potassium voltage-gated channel shaker-related subfamily member 4, potassium voltage-gated channel shaker-related subfamily member 4-like, potassium voltage-gated channel shaker-related subfamily member 5, potassium voltage-gated channel shaker-related subfamily member 6, potassium voltage-gated channel shaker-related subfamily member 7, potassium voltage-gated channel shaker-related subfamily member 10, potassium voltage-gated channel Shab-related subfamily member 1, potassium voltage-gated channel Shab-related subfamily member 2, potassium voltage-gated channel Shaw-related subfamily member 1, potassium voltage-gated channel Shaw-related subfamily member 2, potassium voltage-gated channel Shaw-related subfamily member 3, potassium voltage-gated channel Shaw-related subfamily member 4, potassium voltage-gated channel Shal-related family member 1, potassium voltage-gated channel Shal-related subfamily member 2, potassium voltage-gated channel Shal-related subfamily member 3, potassium voltage-gated channel Isk-related family member 1, potassium voltage-gated channel Isk-related family member 1-like, potassium voltage-gated channel Isk-related family member 2, potassium voltage-gated channel Isk-related family member 3, potassium voltage-gated channel Isk-related family member 4, potassium voltage-gated channel subfamily F member 1, potassium voltage-gated channel subfamily G member 1, potassium voltage-gated channel subfamily G member 2, potassium voltage-gated channel subfamily H (eag-related) member 1, potassium voltage-gated channel subfamily H (eag-related) member 2, potassium voltage-gated channel subfamily H (eag-related) member 3, potassium voltage-gated channel subfamily H (eag-related) member 4, potassium voltage-gated channel subfamily H (eag-related) member 5, potassium inwardly-rectifying channel subfamily J member 1, potassium inwardly-rectifying channel subfamily J member 2, potassium inwardly-rectifying channel subfamily J member 3, potassium inwardly-rectifying channel subfamily J member 4, potassium inwardly-rectifying channel subfamily J member 5, potassium inwardly-rectifying channel subfamily J member 6, potassium inwardly-rectifying channel subfamily J member 8, potassium inwardly-rectifying channel subfamily J member 9, potassium inwardly-rectifying channel subfamily J member 10, potassium inwardly-rectifying channel subfamily J member 11, potassium inwardly-rectifying channel subfamily J member 12, potassium inwardly-rectifying [channe,subfamily] channel subfamily J member 13, potassium inwardly-rectifying channel subfamily J member 14, potassium inwardly-

rectifying channel subfamily J member 15, potassium inwardly-rectifying channel subfamily J member 1, potassium channel, subfamily K member 1, potassium channel subfamily K member 2, potassium channel subfamily K member 3, potassium inwardly-rectifying channel subfamily K member 4, potassium channel subfamily K member 5, potassium channel subfamily K member 6, potassium channel subfamily K member 7, potassium channel subfamily K member 8, potassium channel subfamily K member 9, potassium channel subfamily K member 10, potassium intermediate/small conductance calcium-activated channel subfamily N member 1, potassium intermediate/small conductance calcium-activated channel subfamily member 2, potassium intermediate/small conductance calcium-activated channel subfamily N member 4, potassium voltage-gated channel KQT-like subfamily member 1, potassium voltage-gated channel KQT-like subfamily member 2, potassium voltage-gated channel KQT-like subfamily member 3, potassium voltage-gated channel KQT-like subfamily member 4, potassium voltage-gated channel KQT-like subfamily member 5, potassium voltage-gated channel delayed-rectifier, subfamily S member 1, potassium voltage-gated channel, delayed-rectifier, subfamily S member 2, potassium voltage-gated channel delayed-rectifier subfamily S member 3, potassium voltage-gated channel shaker-related subfamily beta member 1, potassium voltage-gated channel shaker-related subfamily beta member 2, potassium voltage-gated channel shaker-related subfamily beta member 3, potassium inwardly-rectifying channel subfamily J inhibitor 1, potassium large conductance calcium-activated channel subfamily M alpha member 1, potassium large conductance calcium-activated channel subfamily M alpha member 3, potassium large conductance calcium-activated channel subfamily M beta member 1, potassium large conductance calcium-activated channel subfamily M beta member 2, potassium large conductance calcium-activated channel subfamily M beta member 3-like, potassium large conductance calcium-activated channel, potassium large conductance calcium-activated channel sub M beta 4, hyperpolarization activated cyclic nucleotide-gated potassium channel 1, calcium channel voltage-dependent L type alpha 1S subunit, calcium channel voltage-dependent L type alpha 1C subunit, calcium channel voltage-dependent L type alpha 1D subunit, calcium channel voltage-dependent L type alpha 1F subunit, type calcium channel voltage-dependent P/Q type alpha 1A subunit, calcium channel voltage-dependent L type alpha 1B subunit, calcium channel voltage-dependent alpha 1E subunit, calcium channel voltage-dependent alpha 1G subunit, calcium channel, voltage-dependent alpha 1H subunit, calcium channel voltage-dependent alpha 1I

subunit, NES (nestin), scip, sonic hedgehog, Smoothened Shh receptor, Patched Shh binding protein, calbindin d28 K, calretinin, parvalbumin, Trk B, GFR alpha 1, GFRalpha 2, GFRalpha 3, Neurotrophin receptor, Neurotrophin receptor, or Neurotrophic factor receptor.

134 (amended). A transgenic animal comprising two or more transgenes, each said transgene comprising (a) first sequences coding for a selectable or detectable marker protein; and (b) regulatory sequences of a characterizing gene corresponding to an endogenous gene or ortholog of an endogenous gene operably linked to said first sequences such that said first sequences are expressed in said transgenic animal with an expression pattern that is substantially the same as the expression pattern of said endogenous gene in a non-transgenic animal or anatomical region thereof, wherein the characterizing gene is different for each said transgenes, and wherein each said transgene is present in the genome at a site other than where the [endogneous] <u>endogenous</u> gene is located.

146 (amended). A collection of pure populations of cells isolated from the transgenic animals of the collection of lines of transgenic animals of claim 1 or 28, wherein said cells express said detectable or selectable marker and each of said pure [pure] populations is isolated from a transgenic animal having a different characterizing gene.

153. A method of screening a candidate molecule for an effect on one or more cell types, said method comprising

(a) administering said candidate molecule to a transgenic animal from each line of transgenic animals of the collection of transgenic animals of claim 1;

(b) isolating a pure population of cells from each of said transgenic animals that express said first sequences from the cells that do not express said first sequences; and

(c) detecting a change in said pure populations of cells from said transgenic animals [adminstered] <u>administered</u> said candidate molecule in comparison to corresponding pure populations of cells from transgenic animals from said lines of transgenic animals not administered said candidate molecule.